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Effects of intraamniotically administered thyroxin on acceleration of fetal pulmonary maturity in preeclamptic toxemia

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1 Introduction

The role of idiopathic respiratory distress syndrome (IRDS) in perinatal death is proved by data published in various countries [7, 9, 10, 24, 26, 27]. In view of the high incidence of premature births in Hungary as well as observations that it is premature birth above all which predisposes the development of IRDS, steroid prophylaxis remains in the center of professional interest [14, 16, 22, 26, 27]. As numerous side effects and risks for steroid administration is known [10, 18], other possibilities should be investigated for preventive medication. Wu et al. [29, 30] with laboratory animal experiments, Machiach et al. [11, 12, 21] in human subjects proved that other pharmacologic agents can be used. Intraamniotically administered thyroxin beneficially influences the development of pulmonary surfactant, and it is applicable for preventing IRDS. Since 1974 we have regularly used dexamethasone for IRDS prophylaxis; thus, we have had the opportunity to observe that in pregnancy complicated by toxemia, intrauterine death was more frequent following steroid prophylaxis. It seemed reasonable that for IRDS prophylaxis, thyroxin should be administered intraamniotically in pregnancy complicated by preeclamptic toxemia. Our purpose is to report our observations on the effects of intraamniotically applied L-Thyroxin "Henning".

Curriculum vitae

Dr. Iván Veszelovszky was born in 1938 in Zombor, Hungary. He studied medicine at Szeged University, Hungary. After graduation in 1964, he specialized in obstetrics and gynecology in 1968. In 1976 he was appointed as Head of the Department of Obstetrics and Gynecology at the Municipial Hospital, Szentes. He gained a scientific degree (Candidate for Medical Sciences) in 1980. His project was entitled "Prevention of Idiopathic Respiratory Distress Syndrome with Dexamethasone". Since 1985 he has been a titular docent of Szeged University. His main interests are perinatology and amniotic fluid analysis.

2 Material and method

Between January 1, 1982 and January 1, 1984 according to Wittlinger, 18 cases of serious and fairly serious toxemic pregnancy were administered 500 µg of L-Thyroxin "Henning" in a single dose intraamniotically after the laboratory findings of negative pulmonary maturity

in the amniotic fluid. The ages of the patients were between 16 and 39 years with a gestational age of 29–40 weeks (mean: 36.3 weeks). Prior to the considered therapy but after the thorough clinical examinations of the mother, amniotic fluid was obtained by ultrasound-directed transabdominal amniocentesis with a PICKER LS 2700 ultrasound machine. After obtaining 30 ml of amniotic fluid, the needle was left in place with sterile closing. For rapid determination, a Clements test was performed, and in case it showed pulmonary immaturity, via the same needle, 500 µg of L-Thyroxin "Henning" was injected into the amnionic fluid. Removing the needle, the patient was kept under surveillance for 24 hours. Prior to thyroxin treatment, cholesterin test was made from cubital vein and the level of estriol, HPL, as well as T_3 and T_4 were determined by Ria method. The same parameters were examined 1 hour after thyroxin administration as well as every 24 hour interval up to parturition. After delivery, the same parameters were determined as well as the level of T_3 and T_4 from mixed blood from the umbilical cord. Besides the Clements test, as part of amniotic fluid analysis, the L/S ratio, amniocrit, glucose, creatinine, estriol and HPL values were determined. In every case the bacteriological examination of the amniotic fluid was performed. Forty-eight hours after medication the amniocentesis was repeated and the chosen parameters rechecked. When medically indicated, labor was induced. When the maternal/fetal state did not require induction, we awaited the onset of spontaneous labor while performing intrauterine examinations. After delivery T_3 and T_4 levels were determined from mixed cord blood.

During the postnatal period, the neonatologist kept the newborn under strict surveillance to observe any early possible side effects. In the 5th day after delivery, from venous blood, the T_3 and T_4 levels were repeated by Ria method. It was not possible to measure T_3 levels from amniotic fluid because a precipitate was not obtainable from the tube.

The changes of the T_4 level and the L/S ratio in the amniotic fluid as well as that of T_4 in the cord were statistically analyzed by Student's x^2-test.

3 Results

The effect of the intraamniotically administered thyroxin on the various parameters examined is presented in table I. 48 hours after thyroxin administration, the T_4 level of the amniotic fluid showed an increase of extreme degree; the difference was very significant ($p < 0.001$). The maternal T_3 and T_4 levels did not change due to the medication (figure 1).

When the delivery occured 48 hours after medication, the T_4 level gradually decreased in the amniotic fluid, and 5–6 days after thyroxin administration the T_4 levels practically showed the prior value. Forty-eight hours after thyroxin administration the L/S ratio rose more then two times in each case (figure 2).

The T_4 level in the cord blood taken after delivery, increased compared to the basic value but the difference was not significant ($p > 0.05$).

Table I. Effect of intraamniotically given L-Thyroxin "Henning" (500 µg) on the examined parameters.

No change observed after administration of thyroxin	Change observed after administration of thyroxin
Maternal: – pulse – blood pressure – temperature – circumference of neck – level of estriol in urine – T_3 level – T_4 level	
Fetal and amniotic fluid, respectively: – amniocrit – estriol level – creatinine concentration – glucose concentration – FHR	– Clements test (became positive) – L/S ratio (rose) – T_4 level (rose at extreme rate) – T_4 level in cord blood*

* the increase is not significant.

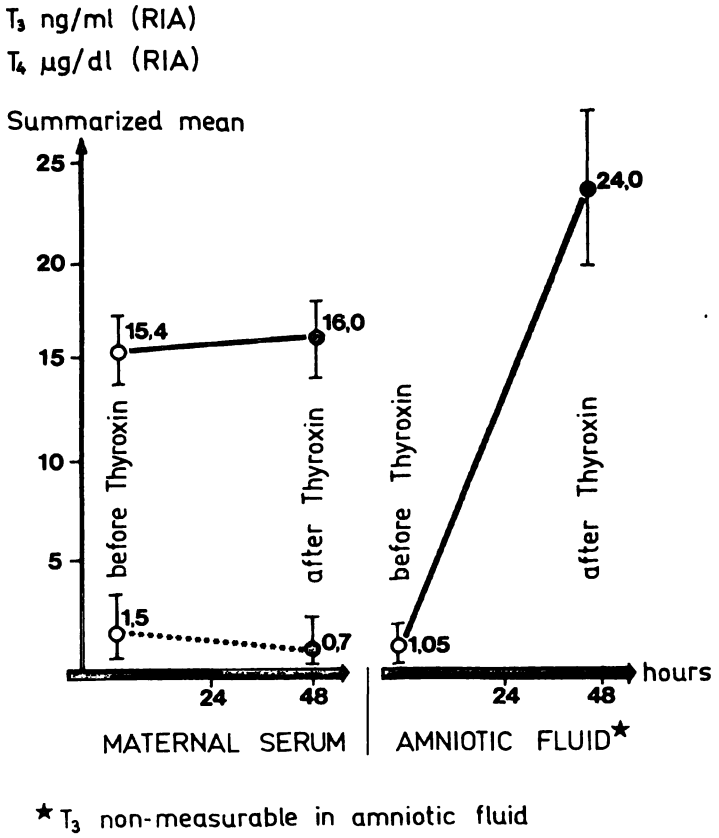

Figure 1. Level of T_3 and T_4 in maternal serum and amniotic fluid after 24—48 hours intraamniotically given 500 µg of thyroxin (n = 18).

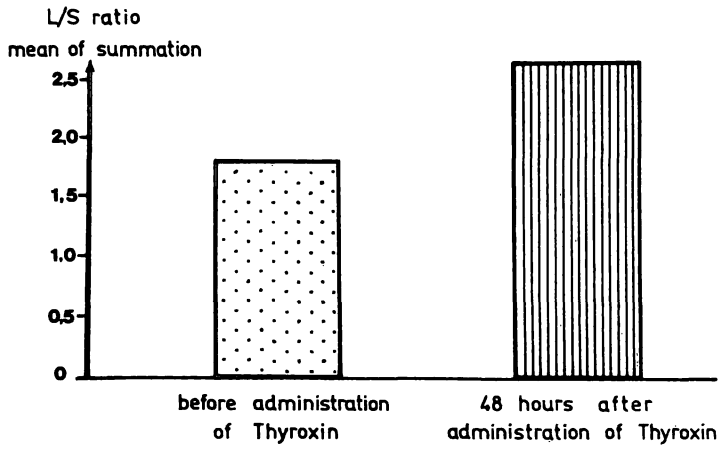

Figure 2. Effect of intraamniotically given thyroxin on L/S ratio.

This may be explained by the fact that the majority of deliveries occured several days after medication. The level of newborn venous blood was also normal in the 5th postnatal day showing euthyreoid values. During neonatal intensive surveillance, no change was observed that could have been due to thyroxin effect.

In the period of investigation, 1584 deliveries were performed, 58 of which were serious and fairly serious toxemic pregnancies as defined by WITTLINGER. Thyroxin was not given in 40 cases for the following reasons: contraindication, premature rupture of membrane, fetal distress, intrauterine death and also when the test of amniotic fluid demonstrated fetal pulmonary maturity. These 40 cases were regarded as the non-treated group. The data obtained from the thyroxin treated group and the non-treated group are presented in table II.

Table II. Important data of the thyroxin treated group and the non-treated group and the neonatal outcome.

	Thyroxin treated group	Non-treated group
Number of pregnant women	18	40
Gestational age at parturition less than 37 weeks	14 (~78%)	31 (77.5%)
Weight at birth under 2500 g	7 (~39%)	12 (30%)
Mean of gestational age	36.3	36.7
Toxemia according to WITTLINGER serious (over 20 points)	12 (~67%)	22 (55%)
Fairly serious (between 15—20 points)	6 (~33%)	18 (45%)
Perinatal loss:	1 (56%)	7 (~175%)
intrauterine	1	5
post partum	—	2
Events of perinatal period:		
Number of newborns	17	35
IRDS development	—	6 (~17%)
Loss of HMB	—	2 (~5%)
Transient hyperbilirubinemia	2 (~12%)	4 (~11%)
Infection in perinatal period	1 (~6%)	2 (~5%)

Although 7 of the 18 thyroxin treated pregnant women were delivered of premature infants, IRDS of HMB was not observed. Among the premature infants of the 40 toxemic pregnant women, who were not treated with thyroxin, IRDS was observed in 8 cases, and 2 of the infants were under 1500 g and died. In both cases the autopsy findings demonstrated hyaline membrane disease (in one of the two the direct cause being intracranial hemorrhage). In this thyroxin-non-treated group 5 additional infants were lost.

Five intrauterine deaths prior to delivery were due to toxemic placental insufficiency according to the autopsy findings.

The details of one of the fetal loss in the thyroxin-treated group are the following:

The gravida was in the 33rd gestational week was hospitalized with the diagnosis of preeclamptic toxemia. The delivery was induced because her blood pressure was 180–190/130 torr despite medication. Her proteiunuria was rapidly progressing (to 28.7 g/day) in the collected urine, and in addition the estriol level was too low for measurement. An amniocentesis was performed before the induction and indicated pulmonary immaturity (Clements test: negative, L/S ratio: 1.2, amniocrit: 0.20, glucose: 2.4 mmol/l, creatinine: 1.375 mmol/l). Thus, thyroxin was given intraamniotically. Twenty-four hours after the medication, her temperature rose and intrauterine death occurred. The fetus weighed 2100 g, and the autopsy could demonstrate only symptoms of intrauterine hypoxia. In this case, a role for thyroxin in the fetal loss cannot entirely be excluded.

4 Discussion

The dangers of preeclamptic toxemia both for the mother and the fetus are well known [2, 4, 18, 23]. One of the most effective means of preventing complications is an induced preterm delivery. The greatest danger of a poorly timed preterm delivery is IRDS, due to pulmonary immaturity. In cases of serious toxemia, after steroid administration, the number of intrauterine deaths rise [2, 10, 18]. In recent years more authors reported that thyroxin stimulated the surfactant production. The role of T_3 and T_4 in fetal development has not been cleared up including the physiology. NIVELON [15] pointed out that T_4 bound to a protein of great molecular weight (TBG) cannot pass through the placental barrier. The level of maternal T_4 can influence that of the fetal's only in early pregnancy (under 18 weeks). He also proved that the T_4 reaches the fetus via the amniotic fluid. The T_4 level of the amniotic fluid can be measured and its changes follow those from the fetal serum level. It was also established that in the fetus, the thyroid hormones favorably influence the growth of the bone structure, the development of the nervous system, the myelinization and increase the production of pulmonary surfactant in the II type pneumocytes [1, 5, 6, 8, 17, 19]. WU, KIKKAWA et al. [29, 30] proved that intraamniotically administered thyroxin increased the pulmonary surfactant level in laboratory animals. The action of mechanism presumably takes effect by accelerating the differentiation of a certain enzymetic system. Observations on patients are not unanimous. Intraamniotically administered T_4 is used not only for IRDS prevention but also for other therapies. WEINER et al. [28] attempted to treat proved fetal goiter in the 30th gestational week by intraamniotically applied T_4. SCHREIER et al. [20] could not observe a decressed incidence of IRDS after intraamniotically administered T_3. MACHIACH et al. [11, 12] reported significantly decreasing incidence of IRDS following intraamniotically administered T_4. DUDENHAUSEN [3] published similar results: after levothyroxin administration the lecithin level in the amniotic fluid significantly increased and, parallel with this, the observed number of hyaline membrane syndrome decreased. However, in the 22 cases examined, on five occasions fetal tachycardia could be observed 2 days after the thyroxin administration. In 1982 we reported [13, 25] favorable results obtained in a few cases; thus the drug has been used in a larger number of cases. On the basis of our results it is concluded that thyroxin, in the applied dose, brings about within 48 hours, an increase in the L/S ratio as well as the Clements test used for determinations of pulmonary surfactant. The other parameters examined in the amniotic fluid, representing functional and somatic maturity, and the hormone estriol, HPL levels indicating the intrauterine state of the fetus, did not change

due to thyroxin. Neither in the mother nor in the newborn was clinical side effect observed due to thyroxin prophylaxis. The T_4 was rapidly eliminated from the amniotic fluid. The post-medication T_4 level in the fetus was gradually decreased depending on the time that elapsed until delivery, and on the 5th to 6th days following the thyroxin administration it was almost normal. On the post-natal 5th day, the T_4 levels of the venous blood taken from the newborn infants did not show any increase. The passage of the drug via amniotic fluid to the fetus presumably stops at the placenta barrier and the thyroxin does not reach the mother. This presumption is supported by the fact that an increased thyroxin level was not observed in the maternal venous blood regardless of the time of administration. The placenta serves as a two-way barrier (mother-fetus, fetus-mother) for the drug. This is supported by our observation that following the intraamniotically administered 500 µg L-Thyroxin, the maternal levels were not altered. In our opinion, in cases of serious and fairly serious preeclamptic toxemia, where the induction of labor is vital, in the interest of the fetus, intraamniotically administered L-Thyroxin can be effectively applied, though a premature birth can be inevitable.

Summary

In 18 cases of serious and fairly serious toxemic pregnancy, the authors gave 500 µg L-Thyroxin "Henning" intraamniotically after the laboratory evaluation demonstrated negative pulmonary maturity from an amniotic fluid sample. Maternal and fetal complications due to the drug could not be observed. Despite a 39% premature incidence, IRDS and hyaline membrane disease were not observed. The administered T_4 caused a positive change in the direction of the L/S ratio and the Clements test. The other amniotic fluid parameters did not change, exept the T_4 level. The extremly high T_4 level obtained 48 hours later gradually became normal several days later. The T_4 values obtained from the blood of the mother and the newborn on the 5th postnatal day were normal. In toxemic cases where the induction of labor is vital and there is a risk of IRDS and steroid application in contraindicated, intraamniotic thyroxin is recommended as prophylaxis for IRDS.

Keywords: Fetal pulmonary maturity, preeclamptic toxemia, thyroxin.

Zusammenfassung

Wirkung einer intraamnialen Thyroxingabe auf die Akzeleration der fetalen Lungenreife bei Präeklampsie
Bei 18 Schwangeren mit schwerer bzw. mäßiger präeklamptischer Symptomatik wurden 500 µg L-Thyroxin „Henning" intraamnial appliziert. Zuvor hatte die laborchemische Untersuchung des Fruchtwassers eine fehlende Lungenreife ergeben. Wir konnten weder bei der Mutter noch beim Feten Komplikationen als Folge der Medikation beobachten. Trotz einer Frühgeburtsinzidenz von 39% trat in keinem Fall ein RDS auf. Das applizierte T_4 veränderte die L/S-Ratio im Fruchtwasser und das Ergebnis des Clements-Tests in positiver Richtung. Andere Parameter im Fruchtwasser veränderten sich mit Ausnahme des T_4-Spiegels nicht. Der extrem hohe T_4-Spiegel nach 48 Stunden normalisierte sich schrittweise einige Tage später. Die T_4-Blutspiegel lagen am 5. Tag post partum bei Mutter und Kind im Normbereich. Ist eine Geburtseinleitung bei Präeklampsie vital indiziert und liegt das Risiko für ein RDS vor, so wird bei Vorliegen einer Kontraindikation für Steroide die Prophylaxe eines RDS mittels intraamnialer Thyroxingabe empfohlen.

Mots-clés: Fetale Lungenreife, Präeklampsie, Thyroxin.

Résumé

Les effets de la thyroxine en injection intra-amniotique sur l'accéleration de la maturité pulmonaire fœtale dans le préeclampsie
Les auteurs ont administré en intra-amniotique 500 µg de L. thyroxin «enning» au cours de 18 grossesses avec toxémie grave ou assez grave après que le laboratoire ait montré une immaturité pulmonaire sur l'analyse du liquide amniotique. Il n'a pas été observé de complications maternelles ou fœtales secondaires au médicament. Il n'a pas été observé non plus de SDR ou de maladie

des membranes hyalines malgré une incidence de prématurité de 39%. La T_4 administrée a positivé le rapport L/S du liquide amniotique ainsi que le test de Clément. Les autres paramètres du liquide amniotique ne sont pas modifiés à l'exception du taux de T_4. Le taux très élevé de T_4 obtenu à 48 heures se normalise ensuite progressivement en quelques jours. Les valeurs de T_4 chez la mère et chez le nouveau-né étaient normales au cinquième jour du post-partum. Dans les cas de toxémie où l'induction du travail est vitale et où il y a un risque de SDR avec contre-indication. aux corticoïdes, les auteurs recommandent l'injection intra-amniotique de thyroxine comme prophylaxie de SDR.

Mots-clés: Maturité pulmonaire fœtale, préeclampsie, thyroxine.

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